Austin Health

Ask an Informationist

Choosing Wisely Australia

FOR ACUTE NON-VARICEAL UPPER GI BLEED...

SHOULD IV PPIs BE GIVEN TWICE DAILY OR CONTINUOUSLY?

Current

2016 | 2002

Globally, guidelines recommend:
in high risk patients, with acute non-variceal UGIB, post endoscopic haemostasis, **administer PPI as IV bolus (80mg) followed by continuous infusion (8mg/hr) for 72 hours**

BSGE 2002; ACG 2012; ESGE 2015; NICE2016; Nanchang 2016; JGES 2016

but wait...

2017

UTD recommends administering IV PPI "at a dose of **40mg twice daily** rather than a high-dose continuous infusion"

*"Our approach differs from 2010 and 2012 guidelines...Meta-analyses of randomised trials have **failed to show superior outcomes with high-dose continuous IV PPI** administration compared with intermittent dosing"*

Overview of the treatment of bleeding peptic ulcers, UpToDate 2017

and...

"intermittent PPI therapy has been found to be safe and effective while significantly reducing cost, even in patients with high-risk stigmata after endoscopy"

Evidence summary - American Journal of Health-System Pharmacy, Feb 2017

plus...

- Low dose IV PPI achieved the **same efficacy** as high dose PPI post endoscopic haemostasis
- "High dose PPI show little or **no difference** in the risk of rebleeding and mortality"
- "The risk/benefit and cost/benefit balance are probably unfavorable to the use of high doses"

Evidence summaries 2010 & 2016

In patients with acute non-variceal upper GI bleed, should PPIs be given twice daily or continuously?

> "The recommendation for high-dose continuous infusion PPIs is based on the hypothesis that maintaining intragastric pH > 6 maximizes clot stabilization and prevents recurrent ulcer bleeding.
> The unresolved question is whether intermittent PPIs are an acceptable alternative to continuous-infusion PPIs."
>
> Source: Annals of Internal Medicine *2015; 162: JC8*

At the request of the Austin Health Choosing Wisely Steering Committee, this report compiles evidence specifically addressing the use of proton pump inhibitors (PPIs) in acute non-variceal upper gastrointestinal bleed (UGIB), post-endoscopic haemostasis. Evidence from the literature that discusses low-risk patients; the use of PPIs pre-endoscopy; or the treatment of UGIB from variceal or other causes, was outside the scope of this report.

Current guidelines

2016

Japan Gastroenterological Endoscopy Society - Guidelines for endoscopic management of non-variceal upper gastrointestinal bleeding*:*

- High-dose IV PPI therapy (80mg bolus followed by 8mg/h continuous infusion for 72hour) after endoscopic haemostasis has been adopted in Western countries and was demonstrated to be superior to placebo/no treatment in reducing the rates of rebleeding, surgery, and mortality.

Source: Digestive Endoscopy 28:–378

NICE clinical guideline - Acute upper gastrointestinal bleeding in over 16s: management

NICE conducted a surveillance report in 2016 to update their 2012 guideline.
"After considering all the new evidence, consultation with stakeholders and views of topic experts, we (NICE) decided that an update is not necessary for this guideline". Therefore, current recommendations are:

- Offer PPIs to patients with non-variceal upper gastrointestinal bleeding and stigmata of recent haemorrhage shown at endoscopy.
- "A regimen of an 80mg bolus of Omeprazole or Pantoprazole followed by a 72hour infusion of 8mg per hour was used in the majority of studies. In contrast studies of orally administered proton pump inhibitor drugs used comparable dosage but a shorter duration of therapy. We are therefore unable to recommend a specific dosage regimen…the Guideline Development Group did not feel able to make a firm recommendation on the preferred route of administration" of PPIs.

Source: National Institute of Health and Care Excellence 2016

2015

Guidelines for the diagnosis and treatment of acute non-variceal upper gastrointestinal bleeding (2015 Nanchang, China)

- "It has been recommended that for high-risk patients after endoscopic hemostasis (e.g. patients with Forrest Ia–IIb ulcers, having problems in endoscopic hemostasis or uncertain endoscopic hemostasis outcomes, concurrently taking anti-platelet drugs or NSAIDs), large-dose intravenous PPIs (such as esomeprazole) should be administered for 72hour"
- "The treatment duration of high-dose PPIs can be extended, and then switched to intravenous infusion of standard-dose PPIs twice daily for 3–5days, and finally to oral administration of standard-dose PPIs, until the ulcer heals."

Source: Journal of Digestive Diseases 2016 Feb;17(2):79-87

Diagnosis and management of non-variceal upper gastrointestinal hemorrhage: European Society of Gastrointestinal Endoscopy (ESGE) Guideline

- "ESGE recommends PPI therapy for patients who receive endoscopic hemostasis and for patients with adherent clot not receiving endoscopic hemostasis. PPI therapy should be high dose and administered as an intravenous bolus followed by continuous infusion (80mg then 8mg/hour) for 72hours post endoscopy (strong recommendation, high quality evidence)"

Source: Endoscopy 2015; 47: 1–46

2012

American College of Gastroenterology - Management of patients with ulcer bleeding

- For active bleeding or non-bleeding visible vessels or adherent clot, a bolus of 80mg proton pump inhibitor followed by continuous infusion of 8mg/hr infusion is to be used.
- Following 72hours of infusion therapy, an oral PPI may be used.
- If the clot is a flat pigmented spot or a clean ulcer base, an oral PPI may be used for management (without infusion) (Laine 2012).

Source: American Journal of Gastroenterology 2012; 107:345–360

Further guidelines:

International Consensus Upper Gastrointestinal Bleeding Conference Group. International Consensus Recommendations on the Management of Patients With Nonvariceal Upper Gastrointestinal Bleeding. Annals of Internal Medicine 2010; 152(2): 101-113

British Society of Gastroenterology Endoscopy Committee. Non-variceal upper gastrointestinal haemorrhage: guidelines. Gut. 2002;51 Suppl 4:iv1–iv6.

Alternative research

2017

Overview of the treatment of bleeding peptic ulcers – UpToDate summary and recommendations

- Patients with active bleeding, a visible vessel, or an adherent clot should continue to receive an IV PPI 72hours following endoscopy.
- We recommend treatment with IV pantoprazole, esomeprazole, or omeprazole (where available) at a dose of 40mg twice daily rather than a high-dose continuous infusion (Grade 1A).

UTD authors note that their approach to proton pump inhibitor administration is based on data from a 2014 meta-analysis and therefore differs from 2012 guidelines:
"Meta-analyses of randomized trials have failed to show superior outcomes with high-dose continuous IV PPI administration compared with intermittent dosing and giving the PPI intermittently rather than as a continuous infusion could decrease resource utilization and cost."
Source: Saltzman, JR. Overview of the treatment of bleeding peptic ulcers. In UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on January 10, 2018)

2016

Optimizing proton pump inhibitor therapy for treatment of non-variceal upper gastrointestinal bleeding

- Although the current guidelines recommend an IV bolus injection followed by continuous infusion of a high-dose PPI, intermittent PPI therapy has been found to be safe and effective while significantly reducing cost, even in patients with high-risk stigmata after endoscopy.
- Regardless of stigmata, after 72hours of IV therapy, patients with UGIB may be safely transitioned to oral PPIs if hemodynamically stable and able to tolerate oral medication.
- As the risk of rebleeding significantly decreases after the first three days, continuation of high-dose therapy beyond 72hours is not necessary in hemodynamically stable patients.

Source: American Journal of Health-System Pharmacy 2017; 74(3): 109-116

Are higher doses of proton pump inhibitors better in acute peptic bleeding?

- Authors reviewed six systematic reviews that together included 27 randomized studies
- Conclude that "high doses of proton pump inhibitors probably result in little or no difference in the risk of rebleeding and mortality. The risk/benefit and cost/benefit balance are probably unfavorable to the use of high doses."

Source: Medwave 2016;16 (Suppl 2):e6476 [article in English/Spanish]

2015

Continuous versus intermittent intravenous pantoprazole for acute gastrointestinal bleeding: a review of the clinical effectiveness and guidelines

- "While the evidence-based guidelines recommended the use of continuous intravenous PPI therapy post endoscopy, in terms of pantoprazole, the evidence from the clinical studies suggested the effect of continuous compared with intermittent intravenous infusion may be similar"
- "Future research, especially with regards to real world observational studies, would help to strengthen the evidence upon which clinical decisions are based"

Source: CADTH 2015

2014

Intermittent vs continuous proton pump inhibitor therapy for high-risk bleeding ulcers: a systematic review and meta-analysis.

- "Intermittent PPI therapy is comparable to the current guideline-recommended regimen of intravenous bolus plus a continuous infusion of PPIs in patients with endoscopically treated high-risk bleeding ulcers"
- … "guidelines should be revised to recommend intermittent PPI therapy"

Limitation of conclusion:
"Our ability to determine the most appropriate intermittent PPI regimen is limited by the variation in intermittent PPI regimens used in the studies included in our systematic review. A variety of dosing schedules and total doses were used, different PPIs were given, and both oral and intravenous routes of administration were used."
Source: JAMA Internal Medicine 2014 Nov; 174(11):1755-62.

2013

Comparison of different regimens of proton pump inhibitors for acute peptic ulcer bleeding

- "There is insufficient evidence for concluding superiority, inferiority or equivalence of high dose PPI treatment over lower doses in peptic ulcer bleeding"
- "By systematically reviewing all available research, we found that the best dose and route of administration of PPIs cannot yet be determined. Our results show that, with regards to deaths, rebleeding episodes, emergency surgeries and need for repeat endoscopic treatments, it is not certain if high intravenous doses of PPIs are more, less or equally effective compared to lower (oral or intravenous) doses of PPIs"

Source: Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD007999.

2010

High-dose vs low-dose proton pump inhibitors for upper gastrointestinal bleeding: a meta-analysis
Conclusion: "The low-dose intravenous PPIs achieved the same efficacy as high-dose PPIs following endoscopic haemostasis in patients with upper gastrointestinal bleeding."

- "A high-dose PPI regimen for patients who have undergone successful endoscopic therapy is not superior to a low-dose PPI regimen for the parameters of rebleeding, the need for surgery, and mortality and rebleeding-related deaths"
- The high-dose PPI regimen did not affect overall mortality
- Subgroup analysis was carried out to determine whether low-dose PPI can have the same efficacy in patients from different regions. This subgroup analysis did not find any difference in rebleeding rate between Asian and European patients using a low-dose PPI regimen

Note: "Regarding the definitions of high and low-dose PPIs, high-dose was not limited to the regimen of 80mg IV bolus followed by an infusion of 8mg/h for 72hour. In our study, dosage of PPI was considered high-dose if at least twice the low-dose of any of the PPIs was used during the 72h following endoscopic hemostasis."

Source: World Journal of Gastroenterology 2010 May 28; 16(20): 2558–2565